

WHAT IS CLAIMED IS:

1. A controlled release preparation comprising tramadol or a pharmaceutically acceptable salt thereof for oral administration.

2. A controlled release preparation as claimed in Claim 1 containing from about 50 to about 800 mg of tramadol (calculated as tramadol hydrochloride).

3. A controlled release preparation as claimed in Claim 1, having an in-vitro dissolution rate (measured by the Ph. Eur. Paddle method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37°C and using UV detection at 270 nm) as set forth below:

<u>TIME (H)</u>	<u>% RELEASED</u>
1	0-50
2	0-75
4	3-95
8	10-100
12	20-100
16	30-100
24	50-100
36	>80

BEST AVAILABLE COPY

4. A controlled release preparation as claimed in Claim 1, having an in-vitro dissolution rate (measured by the Ph. Eur. Paddle method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37°C and using UV detection at 270 nm) as set forth below:

<u>TIME (H)</u>	<u>% RELEASED</u>
1	20-50
2	40-75
4	60-95
8	80-100
12	90-100

5. A controlled release preparation as claimed in Claim 1, having an in-vitro dissolution rate (measured by the Ph. Eur. Paddle method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37°C and using UV detection at 270 nm) as set forth below:

<u>TIME (H)</u>	<u>% RELEASED</u>
1	0-50
2	0-75
4	10-95
8	35-100
12	55-100
16	70-100
24	>90

6. A controlled release preparation as claimed in Claim 1, having an in-vitro dissolution rate (measured by the Ph. Eur. Paddle method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37°C and using UV detection at 270 nm) as set forth below:

<u>TIME (H)</u>	<u>% RELEASED</u>
1	0-30
2	0-40
4	3-55
8	10-65
12	20-75
16	30-88
24	50-100
36	>80

7. A controlled release oral dosage form according to claim 1, comprising a therapeutically effective amount of tramadol or a salt thereof in a matrix adapted to provide a controlled release of the tramadol or salt thereof upon oral administration.

8. A dosage form according to claim 7, wherein said matrix comprises a controlled release matrix comprising at least one alkylcellulose, at least one C<sub>12</sub> to C<sub>36</sub>, aliphatic alcohol and, optionally at least one polyalkylglycol.

9. A dosage form as claimed in claim 8, wherein said optionally at least one polyalkylglycol is polyethylene glycol.

10. A dosage form according to claim 8, wherein said at least one C<sub>12</sub> to C<sub>36</sub> aliphatic alcohol is a C<sub>14</sub> to C<sub>22</sub> aliphatic alcohol.

11. A dosage form according to claim 8, wherein said alkylcellulose is a C<sub>1</sub>-C<sub>6</sub> alkylcellulose.

12. A dosage form according to claim 8, characterized in that the dosage form contains from about 1 to about 20% w/w, preferably from about 2 to about 15% w/w of one or more alkylcelluloses.

13. A dosage form according to claim 8, wherein said aliphatic alcohol is selected from the group consisting of lauryl alcohol, myristyl alcohol, stearylalcohol, cetyl alcohol, ceto-stearyl alcohol, and mixtures of any of the foregoing.

14. The dosage form of claim 13, wherein said aliphatic alcohol is cetyl alcohol or cetostearyl alcohol.

15. A dosage form according to claim 8, wherein said dosage form contains from about 5 to about 30% w/w of aliphatic alcohol.

16. A dosage form according to claim 8, wherein said dosage form contains from about 10 to about 25% w/w of aliphatic alcohol.

17. A dosage form according to claim 1, in the form of film coated spheroids, wherein said spheroid matrix comprises a spheronizing agent, preferably microcrystalline cellulose.

18. A dosage form according to claim 1, in the form of multi-particulates wherein said matrix comprises a hydrophobic fusible carrier or diluent having a melting point from 35 to 140°C and optionally a release control component comprising a water soluble fusible material, or a particulate soluble or insoluble organic or inorganic material.

19. A dosage form according to claims 1, which comprises a tablet formed by compressing a multiparticulate according to Claim 18.

20. A process for the preparation of a solid, controlled release oral dosage form, comprising incorporating a therapeutically effective amount of tramadol or a pharmaceutically acceptable salt thereof in a matrix adapted to provide a controlled release of the tramadol or salt thereof upon oral administration.

21. A process according to claim 20, wherein from about 50 to about 800 mg of tramadol (calculated as tramadol hydrochloride) is incorporated in the dosage form.

22. A process according to claim 20, wherein the dissolution rate (measured by the Ph. Eur. Paddle method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37°C and using UV detection at 270 mm) is as set forth below:

<u>TIME (H)</u>	<u>% RELEASED</u>
1	0-50
2	0-75
4	3-95
8	10-100
12	20-100
16	30-100
24	50-100
36	>80

23. A process according to claim 20, wherein the dissolution rate (measured by the Ph. Eur. Paddle method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37°C and using UV detection at 270 mm) is as set forth below:

<u>TIME (H)</u>	<u>% RELEASED</u>
1	0-50
2	0-75
4	10-95
8	35-100
12	55-100
16	70-100
24	>90

24. A process according to claim 20, wherein the dissolution rate (measured by the Ph. Eur. Paddle method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37°C and using UV detection at 270 nm) is as set forth below:

<u>TIME (H)</u>	<u>% RELEASED</u>
1	0-50
2	0-40
4	3-55
8	10-65
12	20-75
16	30-88
24	50-100
36	>80

25. A process according to claim 20, wherein said matrix comprises a controlled release matrix comprising at least one C<sub>1</sub> to C<sub>6</sub> alkylcellulose, at least one C<sub>12</sub> to C<sub>36</sub>, aliphatic alcohol and, optionally at least one polyalkylglycol.

26. A process according to claim 25, wherein said aliphatic alcohol is a C<sub>14</sub> to C<sub>22</sub> aliphatic alcohol.

27. A process according to claim 25 wherein said optionally at least one polyalkylglycol is polyethylene glycol.

28. A process according to claim 20, wherein said at least one alkylcellulose is ethylcellulose.

29. A process according to claim 20, wherein said dosage form comprises from about 1 to about 20% w/w of one or more alkylcelluloses.

30. A process according to claim 29, wherein said dosage form contains from about 2 to about 15% w/w of one or more alkylcelluloses.

31. A process according to claim 20, wherein said aliphatic alcohol comprises lauryl alcohol, myristyl alcohol or stearyl-alcohol.

32. A process according to claim 31, wherein said aliphatic alcohol is cetyl alcohol or cetostearyl alcohol.

33. A process according to claim 20, wherein said dosage form comprises from about 5 to about 30% w/w of aliphatic alcohol.

34. A process according to claim 33, wherein said dosage form comprises from about 10 to about 25% w/w of aliphatic alcohol.



35. A process according to claim 20, further comprising:

- (a) granulating a mixture comprising tramadol or a pharmaceutically acceptable salt thereof and one or more alkylcelluloses,
- (b) mixing the alkylcellulose containing granules with one or more C<sub>12-36</sub> aliphatic alcohols; and, optionally
- (c) shaping and compressing the granules, and film coating, if desired.

36. A process according to claim 20, further comprising:

- (a) granulating a mixture comprising tramadol or a pharmaceutically acceptable salt thereof, lactose and one or more alkylcelluloses with one or more C<sub>12-36</sub> aliphatic alcohol; and, optionally,
- (b) shaping and compressing the granules, and film coating.

37. A process according to claim 20, further comprising:

- (a) granulating the mixture comprising tramadol or a pharmaceutically acceptable salt thereof and a spheronizing agent;
- (b) extruding the granulated mixture to give an extrudate;
- (c) spheronizing the extrudate until spheroids are formed; and
- (d) coating the spheroids with a film coat.

38. A process according to claim 20, comprising:

- (a) mechanically working in a high-speed mixer, a mixture of tramadol or a pharmaceutically acceptable salt thereof in particulate form and a particulate, hydrophobic fusible carrier or diluent having a melting point from 35 to 140°C and optionally a release control component comprising a water soluble fusible material, or a particulate soluble or insoluble organic or inorganic material at a speed and energy input which allows the carrier or diluent to melt or soften, whereby it forms agglomerates;
- (b) breaking down the larger agglomerates to give controlled release seeds;
- (c) continuing mechanically working with optionally a further addition of low percentage of the carrier or diluent; and
- (d) optionally repeating steps (c) and possibly (b) one or more times.

39. A process according to claim 20, characterized by forming a drug mixture of dry active ingredient and fusible release control materials followed by mechanically working the mixture in a high speed mixer with an energy input sufficient to melt or soften the fusible material whereby it forms particles with the active ingredient.

40. A process according to claim 20, comprising compressing particles obtained by the process of claim 38.

41. A process according to claim 20, comprising compressing particles obtained by the process of claim 39.

00000204-020507  
FUSED-70200860